Analysis of aortic wall stress and rupture risk in patients with abdominal aortic aneurysm with a gender perspective

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Objective: **The most commonly used predictor of rupture of an abdominal aortic aneurysm (AAA) is the diameter; however, this does not estimate the true risk for each patient. Why women with AAAs have an increased growth rate, weaker aortic wall, and increased risk for rupture is yet unclear. It is likely that geometrical and biomechanical properties contribute to found gender differences. Several studies have shown that peak wall stress (PWS) and peak wall rupture risk (PWRR), predicted by a finite element (FE) analysis of AAAs derived from computed tomography (CT), is a better predictor of rupture than maximum diameter. The purpose of this study was to investigate if women with AAAs have an increased PWS and PWRR using an FE model compared to men.**

Method: **Fifteen men and 15 women (AAAs 4-6 cm) were included. AAA geometry was derived from CT scans, and PWS and PWRR were estimated using the FE method. Comparisons were made by *t* test and Mann-Whitney test.**

Results: **Mean age (women 73 years old vs men 71 years old) and mean AAA diameter was similar (49.7 mm vs 50.1 mm) for women and men. PWS did not differ for women 184 and men 198 kPa. PWRR was 0.54 (0.28-0.85) for women and 0.43 (0.24-0.66) for men, $P = .06$.**

Conclusion: **This is the first analysis of stress and strength of the aneurysm wall with a gender perspective. The reported higher rupture risk for women has previously not been tested with geometrical and biomechanical properties. PWS did not differ, but the PWRR was slightly higher in women. However, the difference did not reach statistical significance, probably due to the small sample size. In summary, the results in the present study suggest that differences in biomechanical properties could be a contributing explanation for the higher rupture risk reported for female patients with AAAs. (J Vasc Surg 2011;54:295-9.)**

The most often used predictor for rupture of an abdominal aortic aneurysm (AAA) is its diameter, which allows assessment of the relative rupture risk but not the true individual risk. Two large trials have concluded that an aneurysm diameter of 5.5 cm should be considered as an indication for elective repair in order to prevent rupture.[1,2] There is, however, a need for other predictors for rupture since aneurysms with a diameter <5.5 cm can rupture[3,4] and some aneurysms grow very large without rupture.

Among patients with an AAA <5.5 cm in diameter, women have an increased risk of rupture.[3,5-7] The reasons for this are not yet clear. In line with this, it has been reported that the proportion of women treated for rupture rather than elective repair is larger than for men.[8,9] Risk of aneurysm rupture is a cumulative effect of geometry, tissue properties, and blood pressure. Very few studies investigate these differences from a biomechanical perspective. Consequently, it is still unclear how aneurysm geometry, biomechanical tissue properties, and blood pressure interact, which in turn could quantify the increased risk of rupture in women. From a biomechanical perspective, rupture occurs when the mechanical stress (force per unit area) in the aneurysm wall exceeds the strength at a single site. It has been suggested that peak wall stress (PWS) predicted by a finite element (FE) analysis of AAAs, derived from computed tomography (CT) scan images, is a better predictor of rupture than maximum diameter.[10,11] By adding data on wall strength, the influence of the intraluminal thrombus (ILT) and blood pressure, peak wall rupture risk (PWRR), a parameter which includes both wall stress and strength, can be determined by FE analysis.[12] An ILT is present in most large AAAs[13,14] and its growth and thickness have been suggested to influence the rupture risk of an AAA.[15,16] The predictability of PWS and PWRR improves by including the ILT in the FE analysis because the weakening[17] and thinning[18] of the aneurysm wall underlying the ILT have a major impact, as well as a stress reducing effect since the ILT mechanically unloads the underlying aneurysm wall.

The purpose of this study was to investigate if FE models can confirm the reported higher rupture risk in women, when compared to male patients with aneurysms of the same size. The secondary purpose was to contribute to an increased understanding of a possible gender differ-

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ence in rupture risk by analyzing geometrical and biomechanical properties separately for men and women in a "gender neutral model."

METHODS

Patients. We retrospectively selected a series of 15 women diagnosed with an AAA (4-6 cm) consecutively examined with CT scans 2007 to 2008 and followed at the outpatient clinic at the Karolinska University Hospital, Stockholm, Sweden, and 15 men with AAAs matched on diameter and examined with CT scans during the same time period. Inclusion criteria were an AAA diameter of 4 to 6 cm and having undergone contrast enhanced CT. All patients had a CT as a part of their regular evaluation of their AAA. The available CT examinations were performed on a 4-slice, 16-slice, or 64-slice multidetector CT scanner performed during arterial phase after intravenous contrast injection. One external radiologist reviewed all CT scans. Image analysis was performed on a Picture Archiving and Communication System (Sectra, Linköping, Sweden). Available CT scans of the aorta had slice thicknesses varying from 0.6 to 5 mm between the different examinations. The aneurysm diameters were measured from the outer contours of the enhanced vessel after center-line reconstruction. Blood pressure was recorded at a visit to the outpatient clinic before the CT. The mean arterial pressure (MAP) was calculated from clinic measurements of systolic and diastolic pressure.

Finite element method and image reconstruction. FE analysis divides a complex geometrical structure (eg, AAA) into a finite number of small elements. The elements are connected by nodes, and the network of elements and nodes is called a mesh. The behavior of these individual elements is expressed mathematically and combined to give the behavior of the whole geometry. Wall stress is determined by predicting movement of nodes, which are influenced by the material properties of the AAA and preset boundary conditions.

Aneurysms were reconstructed from contrast enhanced CT scans and analyzed with the diagnostic software A4research (VASCOPS GmbH, Graz, Austria); details are given elsewhere[19] (Fig). PWS and PWRR were calculated from patient-specific FE models, where nonlinear isotropic constitutive descriptions of the wall[20] and ILT[21] as proposed previously are used. The weakening and thinning effect of the ILT on the wall are considered as well as the stress reducing effect since the ILT mechanically unloads the underlying aneurysm wall. An isotropic constitutive description assumes that the stiffness of the tissue is independent from the orientation, (ie, mechanical testing of tissue strips taken at different orientation from the wall would show the same response). An isotropic AAA wall is a usual simplification, although AAA walls show mild anisotropy.[22] The strength of the aneurysm wall was estimated based on a model proposed by Vande Geest et al,[22] which considers geometrical details (local ILT thickness and aneurysm diameter) but also patient-specific information.[23] The parameters of this model are based on in vitro tensile testing of the aneurysm wall, and its application predicts a nonhomogeneous strength of the aneurysm wall, which can be related to the local wall stress to compute a Rupture Risk Index. MAP was used as a pressure loading of the aneurysm and is assumed to reflect an average loading of the aneurysm. Finally, the structural analysis fixes the aneurysm at the renal arteries and the aortic bifurcation; no contact with surrounding organs was considered.

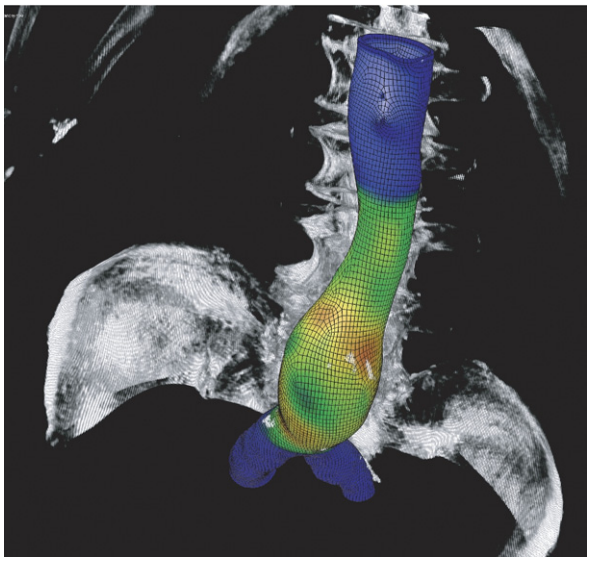

Fig. Reconstructed abdominal aortic aneurysm from contrast enhanced computed tomography (CT) scans, analyzed with the diagnostic software A4research.

PWS is the load in the wall divided by a cross-sectional area (ie, it indicates the loading of the wall). PWRR is computed by relating wall stress to the strength of the wall at that point. For example, if the PWRR is 0.3, the load level is 30% of the strength in that particular point of the wall.

Gender and diameter aspects of the model. Reported in vitro experimental studies did not show a difference in elastic properties of AAA tissue between men and women[20] and consequently the same properties are used for both genders. However, the strength of the AAA tissue in women is lower compared to men.[22] This fact is considered by a reduction of the tensile strength of the wall in women by 191 kPa according to the model proposed by Vande Geest et al.[22] The software in the present study takes this gender difference into account; however, PWS and PWRR predictions are based on both geometrical and biomechanical properties of the aneurysm. Geometrical properties define the geometry of the aneurysm (eg, maximum diameter, ILT volume, ILT thickness, and wall thickness). Biomechanical properties define the mechanical conditions of the AAA (ie, stress in the wall). To investigate this interrelation deeper, we therefore additionally performed an FE analysis where female patients were analyzed with "male tissue properties," (ie, comparing men and women

Table I. Patient characteristics

	Gender		P
	Men	*Women*	*value*
Age (mean)	71 (58-83)	73 (66-84)	.42
Aneurysm diameter (mean)	50.1 (43.6-57.1)	49.7 (40.2-57.2)	.83
MAP (median)	102 (77-110)	100 (80-122)	.21

MAP, Mean arterial pressure.
Aneurysm diameter is given in mm. MAP is given in mm Hg. Range within brackets. Age is given in years.

with the same tissue properties). This especially designed group was denoted as the "gender neutral group," and like all geometrical properties, the ILT will of course not be affected by the transformation. A general comparison of "small" (diameter 40-50 mm) vs "large" (diameter more than 50 mm) aneurysms was also performed in order to test the model in this respect.

Data analysis. On the CT scans, the aorta was segmented between the renal arteries and the aortic bifurcation and reconstructed in 3 dimensions, hence all geometrical (aneurysm diameter, ILT volume) and mechanical (PWS, PWRR) determinants were derived. Gender comparisons and comparisons between small and large aneurysms were performed by independent *t* test for all variables, except MAP, which not was normally distributed and was analyzed with Mann-Whitney test. Statistical significance was defined as $P < .05$.

RESULTS

There was no difference in mean age (73 vs 71 years; $P = .42$), mean aneurysm diameter (49.7 vs 50.1 mm; $P = .83$), or median MAP (100 vs 102; $P = .21$) between women and men (Table I).

PWS was similar for women and men; 184 vs 198 kPa ($P = .42$; Table II). Mean PWRR was 0.54 for women and 0.43 for men, $P = .06$; Table II). There were no gender difference in mean ILT volume between women and men; 42,070 vs 45,008 mm^3 ($P = .81$; Table II).

Patients with larger diameters (>50 mm) had higher mean PWS (211 vs 168 kPa; $P = .01$) and mean PWRR (0.55 vs 0.41, $P = .01$; Table III). There was no difference in the gender distribution between these groups; 7 women and 7 men had a diameter of 40 to 50 mm and 8 women and 8 men had a diameter larger than 50 mm.

In the FE analysis of the gender-neutral group (ie, where female patients received the same biomechanical properties as men), no difference in mean PWRR between women (gender neutral group) and men (0.38 vs 0.43; $P = .24$) was found (Table IV). The mean PWS in this analysis was similar; 179 for women and 198 kPa for men ($P = .28$; Table IV).

DISCUSSION

This is the first comprehensive biomechanical analysis of AAA with a gender perspective (ie, investigating reasons for the increased risk for aneurysm rupture in women using detailed FE models). Although it has been suggested, based on FE models,[24] and shown in vitro that women have a weaker AAA wall,[23] the increased risk for aneurysm rupture in women has not been demonstrated by integrating this information. PWS did not differ for women and men in the present study, whereas there was a trend to higher PWRR in women, however, only borderline significant. Interestingly, the gender difference in PWRR disappeared when women were assigned the same biomechanical properties as men in the analysis.

Few biomechanical studies of AAAs include a gender analysis. Female patients with AAAs have an increased risk for rupture and rupture at a smaller diameter than men.[3,5-7] Reports have also shown an increased aneurysm growth rate for women compared to men,[25-27] which could be a surrogate marker for increased rupture risk. It is shown that for 2 patients with identical AAAs, a woman will have an aneurysm wall that is globally weaker compared to a man.[23] The software in the present study takes this gender difference into account. However, an FE analysis is based on both geometrical and biomechanical properties of the AAA.

Women had a slightly higher PWRR compared to men. The difference did not reach statistical significance ($P = .06$), which may be caused by small sample sizes. We also investigated a "gender-neutral group" where female patients received the same biomechanical properties as men (ie, comparing men and women with the same biomechanical properties and not taking into account that women have a globally weaker AAA). The difference in PWRR disappeared, indicating that geometrical properties alone do not explain the higher rupture risk for female patients with AAAs. The results in the present study suggest that differences in biomechanical properties could be the explanation for the higher rupture risk in female patients with AAAs.

The geometry and its influence on rupture risk has been debated, the main conclusion would today, however, be that tortuosity does not increase the rupture risk.[28] Aortic aneurysms in women as compared to men are usually described as having a more complex anatomy, especially more complex proximal neck anatomy.[29-31] Tortuosity is not the most influential risk for rupture, and our data cannot explain the previously reported higher rupture risk in women by more complex geometry as compared to men.

The ILT is considered to influence the natural history of an AAA and affects the vessel wall in different ways. The ILT has characteristic solid mechanical properties[21] and has an impact on the biomechanical properties[32,33] by influencing stress magnitude and distribution.[34,35] The ILT influences the proteolytic degradation of the underlying aneurysm wall.[18] The AAA wall adjacent to regions of thicker ILT is weaker and to a higher extent is affected by cellular hypoxia compared to the wall adjacent to a thinner layer of ILT.[17] Clinical studies have demonstrated that the growth rate of the ILT may be a predictor of rupture.[15] In a recent study, an evaluation of a rupture risk prediction was performed by comparing PWS and PWRR.[36] Inclusion of

Table II. PWS, PWRR, and ILT volume in men and women

Biomechanical properties	*Gender*		P *value*
	Men	*Women*	
PWS (kPa, mean)	198 (111-266)	184 (120-282)	.42
PWRR (mean)	0.43 (0.24-0.66)	0.54 (0.28-0.85)	.06
ILT (mm^3, mean)	45,008 (2371-114,679)	42,070 (714-83,361)	.81

ILT, Intraluminal thrombus; *PWRR*, peak wall rupture risk; *PWS*, peak wall stress.
Range within brackets.

Table III. PWS and PWRR in small (≤50 mm) and large (>50 mm) aneurysms

Biomechanical properties	*Diameter*		P *value*
	≤50 mm	*>50 mm*	
PWS (kPa, mean)	168 (111-225)	211 (131-282)	.01
PWRR (mean)	0.41 (0.24-0.59)	0.55 (0.29-0.85)	.01

PWRR, Peak wall rupture risk; *PWS*, peak wall stress.
Range within brackets.

Table IV. "Gender-neutral group"; PWS, PWRR, and in men and women

Biomechanical properties	*Gender*		P *value*
	Men	*Women ("gender neutral group")*	
PWS (kPa, mean)	198 (111-266)	179 (120-282)	.28
PWRR (mean)	0.43 (0.24-0.66)	0.38 (0.22-0.59)	.24

PWRR, Peak wall rupture risk; *PWS*, peak wall stress.
Range within brackets.

the ILT in the FE model significantly increased the predictability of the biomechanical simulation. PWRR was superior in predicting rupture risk compared to PWS when including the ILT and wall thickness in the model. In another recent study, the authors also concluded that the effect of the thrombus on wall stress should be included in the analysis.[37] One could suspect that a relatively larger ILT in women compared to men could be a contributing factor explaining the higher rupture risk in women. However, our data did fail to show such a gender difference.

The present study used mean instead of systolic arterial pressure to predict PWS and PWRR, because it has been demonstrated that diastolic but not systolic hypertension has a significant impact on rupture risk of an AAA.[38] Although the applied FE models considered a nonhomogeneous wall thickness, patient-specific data could not be used and women might have a different aneurysm wall thickness than men. The aneurysm wall shows mild anisotropy[22] but an isotropic material description as proposed earlier[20] has been used in the present study. Calcifications were not considered in the analysis, which may increase the PWS[39]; however, their thorough consideration would also require an appropriate adjustment of the wall thickness. Biological (biochemical) factors related to AAA development and rupture were not considered in the present study; however, to some extent these effects are implicitly included by considering the weakening effect of the ILT on the wall.

CONCLUSION

PWS did not differ, but there was a trend to higher PWRR in women compared to men. When including the same biomechanical properties for men and women in the FE model there were no differences in PWRR. In summary, the results in the present study suggest that geometrical or ILT volume differences between female and male patients with AAAs do not explain the higher rupture risk described in women. Future studies regarding gender differences in rupture risk for patients with AAAs should probably more intensely focus on biomechanical properties.

AUTHOR CONTRIBUTIONS

Conception and design: EL, CG, JS, RH
Analysis and interpretation: EL, FL, CG, JS, RH
Data collection: EL, FL, CG
Writing the article: EL, FL, CG, JS, RH
Critical revision of the article: EL, FL, CG, JS, RH
Final approval of the article: EL, FL, CG, JS, RH
Statistical analysis: EL
Obtained funding: JS, RH
Overall responsibility: RH

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